# Synthesis of All-Methylated Isorugosin B

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**All-methylated isorugosin B was synthesized *via* two-step esterification between optically active valoneic acid and glucose derivatives.**

**Key words** ellagitannin; palladium; coupling reaction; natural product; glucose derivative

Ellagitannins are a class of polyphenols that are suspected of being useful medically, as they are strong antioxidants[1—3]; however, compared to other polyphenols, few synthetic studies of ellagitannins[4—8] have been conducted because of their chemical instability and structural intricacy. Within the ellagitannin family, compounds that contain valoneoyl groups are frequently found in natural products.[9—13] Despite this, the complete synthesis of an ellagitannin containing a valoneoyl group has not yet been reported.

Recently, we reported the stereoselective synthesis of a valoneic acid derivative, in which Bringmann's "lactone concept"[14—18] was used to form its optically active biphenyl moiety.[19] In this paper, based on our previous work, we report the synthesis of all-methylated isorugosin B (**1**)[20—23] (Fig. 1).

The retrosynthetic analysis of **1** is depicted in Chart 1. Two ester functions would be formed in the final stage of the synthetic scheme, leading to the valoneic acid derivative (**2**) and sugar moiety (**3**).[24] The optically active valoneoyl group **2** would be formed by Bringmann's method[4] which involves the intramolecular biaryl coupling reaction[25] of **4**, followed by enantioselective lactone ring opening. The key intermediate **4** would be derived from the corresponding phenol **5** and carboxylic acid **6**.

Initially, we attempted to prepare the biphenyl ether from the Ullmann condensation reaction[26] between methyl *o*-bromobenzoate **7** and (siloxymethyl)phenol **8**.[27] Because the only compound isolated in the reaction between **7** and **8** was the unexpected aldehyde **9**, accompanied by many by-products, we postulated that the formyl compound **10**[27] could be used in the same reaction. Based on this, the desired ether compound **9** was obtained successfully. The reduction of the formyl group and deprotection of the benzyl group afforded the benzyl alcohol **11** (Chart 2).

Protection of the benzylic hydroxyl group of **11** using the *tert*-butyldimethylsilyl chloride (TBSCl)-imidazole system was effective for preparing the phenol fragment **5**. The simple esterification between **5** and the corresponding benzoic

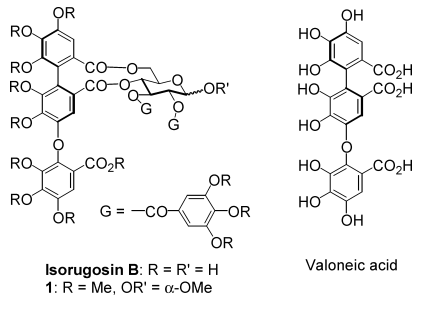


Fig. 1. Structure of Isorugosin B and Its Related Compounds

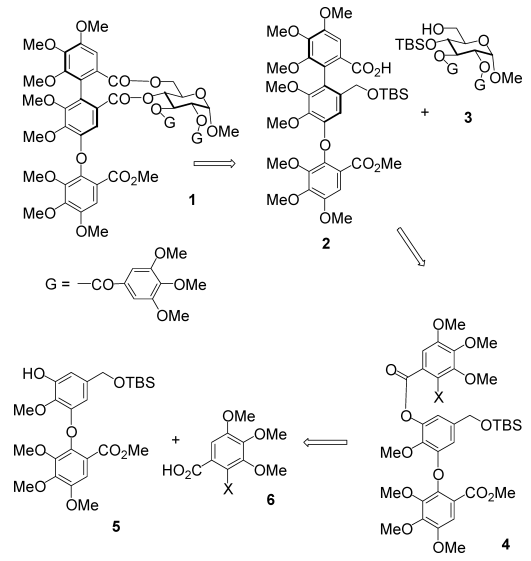

Chart 1. Synthetic Plan for **1**

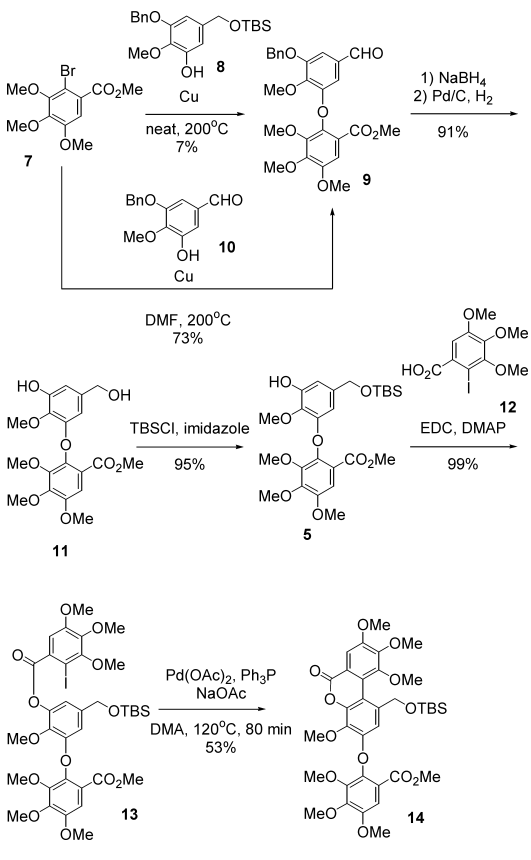

Chart 2. Synthesis of **14**

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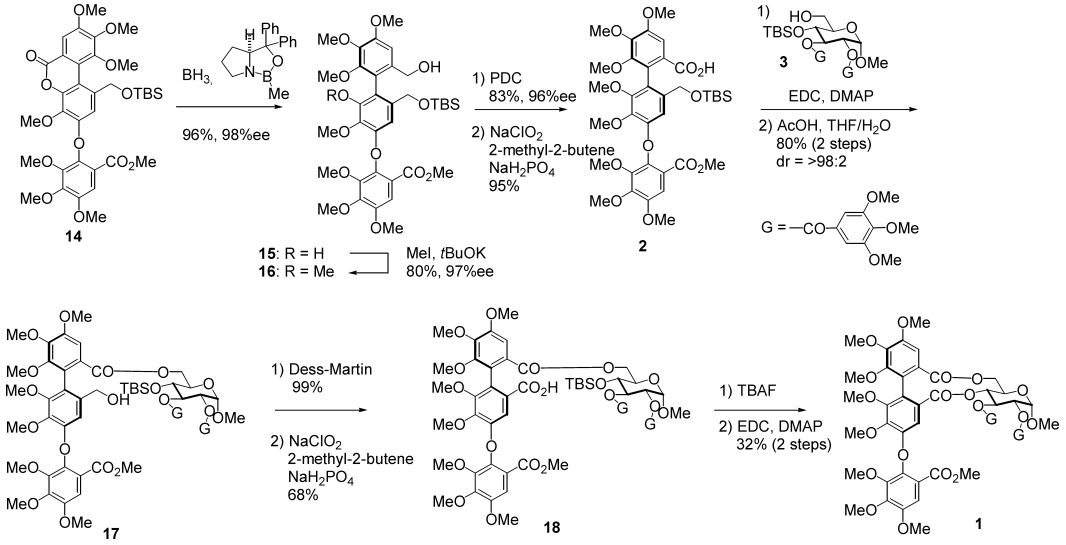


Chart 3. Synthesis of All-Methylated Isorugosin B (**1**)

acid **12** successfully afforded the precursor **13** for the intramolecular biaryl coupling reaction. The reaction of **13** with $Pd(OAc)_2$, $Ph_3P$, and NaOAc proceeded smoothly, resulting in the lactone compound **14** in moderate yield.

The enantioselective lactone-opening reaction of **14** using Bringmann's method, the borane-CBS reagent system,[28] proceeded efficiently to generate the biphenyl compound **15**[29] in an enantioselective form.[30] The methylation of the resulting phenolic hydroxy group followed by two-step oxidation (pyridinium dichromate (PDC) oxidation and Pinnick oxidation[31]) of the benzylic hydroxy group formed the optically active valoneic acid derivative **2** (Chart 3).[30]

To complete the synthesis of **1**, we needed to form the eleven-membered ring *via* double esterification between **2** and the glucose derivative **3**. The first ester condensation between **2** and **3**, and the selective desilylation of the primary alcohol yielded the desired alcohol **17**. This compound was successively subjected to the usual manipulation involving the two-step oxidation leading to the carboxylic acid **18**. Finally, the silyl group on the sugar moiety was deprotected, and this was followed by the second esterification[32] of the hydroxyl group at the 4-position of the sugar with the carboxylic acid of the valoneoyl group, resulting in the synthesis of **1**.[20,33]

The NMR data of the synthetic **1** were identical with the authentic chart.

In conclusion, we succeeded in the first synthesis of the valoneoyl group-containing ellagitannin derivative **1**. Based on this work, our laboratory is attempting to synthesize natural isorugosin B.

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32) The low yield of this step may be due to the low reactivity of the secondary hydroxyl group.
33) The $[\alpha]_D$ value of the synthetic sample did not match the reported value (synthetic $[\alpha]_D$ $+28°$ ($c=1.52$, acetone); reported $[\alpha]_D$ $-7°$ ($c=0.3$, acetone)[20)]). We speculate that this discrepancy was due to impurities in the reported sample, as many unidentified peaks are seen in the authentic NMR data.